Declaration Under 37 CFR 1.132

1. I, Brassel Friedhelm, am the sole inventor of U.S. Application Number 10/541,277.

2. I am an presently employed as Head of Department at the Clinic for Radiology and Neuroradiology in Duisburg, Germany. My CV is attached.

3. I have reviewed the Office Action of June 6, 2009, Rump (Eur. J Clin Pharmacol (2002) 58: 459-465), Doerfler (Neuroradiology 2001, 43, 1112-1117), and the pending claims. I have been informed by counsel that claim 20 has been canceled and its feature added to claims 17 and 22.

4. Rump teaches a ratio of ethibloc, lipiodol, and ethanol that is outside of the claimed range in amended claims 17 and 22.

5. Rump uses a 5-6 French catheter, and teaches use of a 3 French catheter where "catheterization proved impossible."

6. I have carried out embolizations that have a ratio of ethibloc, lipiodol, and ethanol within the range claimed in amended claims 17 and 22. These embolizations were successfully performed in a conventional in vitro avm-flow model. Injections of my emulsions proved to be safe even when injected through the smallest and/or softest flow-directed and guidewire-directed microcatheters (Tracker-10, Boston Scientific, Prowler-10, Cordis, Magic-1.5 and -1.2F, Balt). In contrast to Doerfler et al. (Neuroradiology 2001, 43, 1112-1117), embolizations that have a ratio of ethibloc, lipiodol, and ethanol within the range claimed in amended claims 17 and 22 were done in numerous cases without rupture of the microcatheters with 1.5F or even smaller (1.2F Magic flow-guided microcatheter, Balt). I have obtained best results with a ratio of 30 to 40 % ethibloc, 35 to 30 % lipiodol and 35 to 30 % ethanol.

7. I have performed numerous successful embolizations (that have a ratio of ethibloc, lipiodol, and ethanol within the range claimed in amended claims 17 and 22) in patients with the above mentioned microcatheters. Disadvantages of other at the time available liquid embolic materials like acrylic glue (risk of catheter-glueing in the vessel, low viscosity with small time window for the injection resulting in a lack to control the embolization, release of heat to the vessel due to the exotherm polymerization of acrylic glue) or genuine ethibloc (not homogenized, resulting in unpredictable behaviour during embolization), warmed ethibloc [Doerfler et al. (Neuroradiology 2001, 43, 1112-1117) report to warm genuine ethibloc up to 37°C which leads to a vaporization of the alcohol out of the genuine ethibloc changing the emulsion to an unstable suspension], ethibloc mixed with oily contrast medium – e. g. lipiodol – (changes the genuine ethibloc emulsion to a suspension with rapid separation of the oily contrast medium from the genuine ethibloc during embolization) and the combination of ethibloc warmed to 37°C mixed with lipiodol as used by Doerfler et al. (leading to rupture of flow-guided microcatheters) thus were avoided.

8. I have found that unlike the 3 and 5-6 French catheters of Rump, a much smaller catheter, about 1.2 French, can be used. In experiments, I successfully used a 1.2 French catheter. This catheter allows for reaching much smaller vessels. The 3 and 5-6 French catheters of Rump and his ethibloc (8 ml) / lipiodol (1.5 ml) / ethanol (1.5 ml) mixture is suitable for proximal vessel occlusions as mentioned in this paper ["The chemoembolization treatment consisted of the use of polyvinylalcohol microspheres (ITC-Contour, diameter 150-250 μm, irreversible vessel occlusion, 20 mg MMC 15 patients) followed by sealing of the supplying artery with ethibloc", see Rump, p. 469, l. col., 2nd

para.]. I have found that only mixtures in the range of 30 to 70 % v/v of ethibloc allow an occlusion of smaller plexiform vessels of arteriovenous shunts and vessels of highly vascuralized tumours.

9. I found that unlike the 3 and 5-6 French catheters of Rump, a much smaller catheter, about 1.2 French, can be used (e.g. Magic 1.2F by Balt, France) when using a ratio of ethibloc, ethanol and lipiodol as claimed in amended claims 17 and 22. In numerous experiments and for therapeutic purposes, I successfully used the 1.2 French catheter. This flow-guided catheter allows for reaching much smaller vessels.

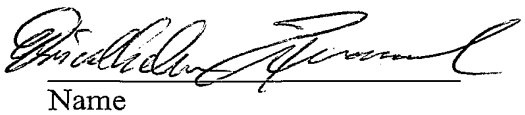
10. In in vitro experiments with an avm-model perfused with fresh pork blood, I found that I had a far wider window of time (up to 30 minutes) where a substantial precipitation or separation of my mixture was not observed. Stop-and-go embolizations even with 1.2 French microcatheters over up to 30 minutes were done in numerous treatments without occlusion or rupture of the microcatheter.

11. I found that despite the high dilution with ethanol, sufficient viscosity is obtained for a successful embolization. Even plexiform small tumour vessels are embolized.

12. Doerfler teaches use of an additional amount of lipiodol to lower the viscosity of the ethibloc. The mixture of ethibloc and lipiodol has a severe disadvantage in that it results in a suspension which rapidly separates. Rapid separation (pure ethibloc with pure lipiodol) can be a problem during injections particularly in small microcatheters. The separation increases from the proximal part of the microcatheter to the distal part. Alternating phases of separated pure ethibloc and lipiodol exit the tip of the microcatheter. Lipiodol passes the arteriovenous border without effect for the embolisation. The phases of highly viscous pure ethibloc increase the risk of occlusion and following rupture of small and soft microcatheters at their most flexible and weakest part which is proximal to the catheter tip (proved by Doerfler), if the operation takes a long time.

13. The combination of Rump and Doerfler fails to teach the claimed invention. The ratios of component to each other in Rump and Doerfler is different, and there is no teaching which components to modify. Even if the modification were done solely according to Rump, the ratios would still not overlap with the claimed ratios. Lastly, the combination of these references does not teach that a small 1.2 French catheter can be used by modifying the ratios, and a long window of time can be obtained for the operation, and that despite the additional dilution, there is sufficient viscosity to obtain a successful embolization.

14. The undersigned declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the life so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and this such willful false statements may jeopardize the patentability of the application or any patent issuing thereon.



Name
Title
Prof. Dr. med. Friedhelm Brassel

February, 18th 2010
Date

CURRICULUM VITAE

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1998–2000: Dept. of Neuroradiology, Hannover Medical School, Germany

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